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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KIM, TAEYOON	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,647	THIRUVENGADAM ET AL.	
	Examiner	Art Unit	
	Taeyoon Kim	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-34,38,44-46 and 48-51* is/are pending in the application.

4a) Of the above claim(s) *1-26,33,34,38,44,46 and 48-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-29,31,32 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The declaration under 37 CFR 1.132 filed 8/31/07 is insufficient to overcome the rejection of claims 27-32 and 45 based upon El-Mallakh et al. in light of Garrahan et al. or Antia et al. as set forth in the last Office action.

In the declaration, applicant discussed the effect of the presence of potassium to the membrane potential ratio obtained in the presence of a compound altering Na+K+ ATPase activity, such as gramicidin or ethacrynate, over in the absence of the compound, and showed the deficiency of significant difference between the ratio calculated from the measured membrane potential in control and bipolar patients under the condition. The data shown in the declaration are credible. However, the showing of such evidence does not obviate 35 U.S.C.§103 rejection made in the previous office action. The method of currently claimed and that of the prior art are mainly based on the ratio obtainable from the various measurements under various different conditions. Since the ratio can be obtained comparing under the different conditions with various parameters, and the use of activator and the presence or absence of potassium in the cell culture medium prior to the measurement of membrane potential are well known in the art as such parameters (based on El-Mallakh et al. and Garrahan et al.), a person of ordinary skill in the art would be able to measure membrane potentials of cells (leukocytes as disclosed in El-Mallakh et al.) under various different combinations of parameters (presence/absence of potassium or the activators), and able to pick and choose the measured membrane potentials to obtain any meaningful ratio comparable

between control (normal) and bipolar patients. The data presented in the declaration may be unexpected under the assumption that such comparison would produce any significant difference between normal and affected subject. However, considering inconsistent and controversial results obtained by various different researchers, there is no indication whether or not such expectation that there would be significant difference between control and bipolar patient when the membrane potential is measured in the presence of potassium. For example, Buss et al. teach there is no significant difference between normal and bipolar patient in their membrane potential ratio obtained by comparison with or without a Na+K+ ATPase activator. Since the method utilized in Buss et al. is basically the same as the method of El-Mallakh et al. as well as the claimed invention, the result of Buss et al. would not reasonably allow to expect that the measurement of membrane potential ratio disclosed in the declaration would differentiate normal vs. bipolar disorder. Therefore, the current declaration would not be considered to present unexpected results of the method.

Response to Arguments

Applicant's arguments with respect to claim rejection under 35 U.S.C.§112, 1st paragraph, have been fully considered and are persuasive. The rejection of claims27-32 and 45 under 35 U.S.C.35 U.S.C.§112 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-29, 31, 32 and 45 are rejected under 35 U.S.C. 112, second

paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "fresh" in claims 27-29, 31, 32 and 45 is a relative term which renders the claim indefinite. The term "fresh" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-29, 31, 32 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The term "fresh" in the amended claims introduces a new matter situation. The specification does not have an adequate disclosure to support this limitation ("fresh cells").

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-29, 31, 32 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over El-Mallakh et al. (1996) in view of Garrahan et al. (1967) or Antia et al. (1995).

Claims 27-29, 31, 32 and 45 are drawn to a method for diagnosing a bipolar disorder by comparing ratios of the mean membrane potential in the presence and absence of a compound altering sodium pump of a patient with the ratios from both positive and negative control, and under the condition of the presence or absence of potassium. The claims also disclose a variety of different compounds altering the activity of sodium pump including ethacrynate.

El-Mallakh et al. teach a method of measuring transmembrane potential (TMP) from leukoblasts isolated from bipolar patient and control in the absence or presence of gramicidin, the relative TMP, calculated from the ratio of TMP in the absence and TMP in the presence of gramicidin (depolarizing agent), and then compares the difference to distinguish the patient and the control (whole document; especially see p.199, 2.3. TMP

measurement).

Although El-Mallakh et al. do not particularly teach the use of various combination of presence or absence of potassium during the measurement, it would have been obvious for a person of ordinary skill in the art to utilize various different conditions including in the presence or absence of potassium ion (see Garrahan et al.). This is because the ratio of TMP obtained in the absence of potassium would provide better understanding of the activity of sodium pump, and would provide additional data for the comparison between a patient and controls. Thus, a person of ordinary skill in the art recognizes the condition of the absence of potassium as a parameter to optimize the outcome of the method of El-Mallakh et al. to distinguish the difference between a bipolar patient and control.

The US Federal Circuit has recently explicitly stated that in order to make a *prima facie* case of obviousness, the suggestion and motivation to combine said references need not be explicitly stated in the text of the references. Rather, consideration of common knowledge and common sense when combining references is not only permitted *but required*. See DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 80 USPQ2d 1641 (Fed. Cir. 2006) which states:

> ""Suggestion" test for obviousness does not require that suggestion, teaching, or motivation to combine cited prior art references be found in references themselves, or that such suggestion or motivation be explicitly stated; suggestion test is flexible rather than rigid and categorical, recognizing motivation to combine found in knowledge of persons of ordinary skill in art or nature of problem to be solved, as well as in references, and test not only permits, but requires, consideration of common knowledge and common sense."

Although El-Mallakh et al. do not teach the use of ethacrynate, it is well known in

the art that ethacrynate is a compound to activate sodium pump as supported by Antia et al., and therefore considered as an art-recognized equivalent to gramicidin used in the method of El-Mallakh et al. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945) (Claims to a printing ink comprising a solvent having the vapor pressure characteristics of butyl carbitol so that the ink would not dry at room temperature but would dry quickly upon heating were held invalid over a reference teaching a printing ink made with a different solvent that was nonvolatile at room temperature but highly volatile when heated in view of an article which taught the desired boiling point and vapor pressure characteristics of a solvent for printing inks and a catalog teaching the boiling point and vapor pressure characteristics of butyl carbitol. "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)".

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

In the response to the previous office action, applicant argued that El-Mallakh et al. failed to disclose comparing its relative TMP to another sample. Although this argument is vague, the examiner considers that this argument is based on individual ratio (current claim) vs. pooled ratio (reference). It is acknowledged that El-Mallakh et al.

disclose the demographic data pooled from individual subjects as argued by applicant. However, it would have been obvious that to obtain the demographic data, a TMP is measured from cells extracted from each individual, and also obvious to compare each TMP measured to another samples. Therefore, the argument that El-Mallakh et al's method failed to compare individually to each other is not persuasive.

Applicant argued that the reference of El-Mallakh et al. fails to disclose comparing the relative TMPs for the purpose of diagnosing a bipolar disorder. This is not persuasive because it is obvious to a person of ordinary skill in the art that the measurement and the analysis disclosed in El-Mallakh et al. is ultimately for the diagnosis of bipolar disorder, the method of El-Mallakh et al. in view of secondary references would carry out the intended purpose of diagnosing a bipolar disorder.

With regard to the unexpected result, the Applicant's attention is directed to the discussion above under the section of "Response to Amendments".

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taeyoon Kim whose telephone number is 571-272-9041. The examiner can normally be reached on 9:00 am - 5:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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